

26/27. (New) A method of synthesizing a modified therapeutic peptide capable of forming a peptidase-stabilized therapeutic peptide conjugate, the peptide comprising between 3 and 50 amino acids and having a carboxy terminal amino acid, an amino terminal amino acid, a therapeutically active region of amino acids and a less therapeutically active region of amino acids the method of comprising the steps of:

- a) if the therapeutic peptide does not contain a cysteine, then synthesizing the peptide from the carboxy terminal amino acid or the amino terminal amino acid, and coupling a reactive group, either directly or via a lysine, to the carboxy terminal amino acid, to the amino terminal amino acid, or to an amino acid, or to an amino acid comprised between the carboxy terminal amino acid and the amino terminal amino acid, the reactive group reacting with amino groups, hydroxyl groups or thiol groups on blood component to form a covalent bond therewith;
- b) if the therapeutic peptide contains only one cysteine, then synthesizing the peptide in accordance with step a) while providing the cysteine in a protected form, the cysteine remaining protected prior to and after coupling, either directly or via a lysine, of the reactive group to the peptide;
- c) if the therapeutic peptide contains two cysteines, synthesizing the peptide in accordance with step a), and either
 - i) cleaving the peptide from the resin, oxidizing the two cysteines to form a disulfide bridge, and coupling the reactive group to the peptide, either directly or via a lysine; or
 - ii) oxidizing the two cysteines to form the disulfide bridge, coupling the reactive group to the peptide, and cleaving the modified therapeutic peptide from the resin; or
 - iii) coupling the reactive group to the peptide, either directly or via a lysine, cleaving the peptide from the resin, and oxidizing the two cysteines to form the disulfide bridge;or
 - iv) coupling the reactive group to the peptide, either directly or via a lysine, oxidizing the two cysteines to form the disulfide bridge, and cleaving the modified peptide from the resin;
- d) if the therapeutic peptide contains more than two cysteines, synthesizing the peptide in accordance with step a), optionally cleaving the peptide from the resin, sequentially and selectively oxidizing each pair of cysteines to form disulfide bridges, and, if the number of cysteines is odd, protecting the last cysteine remaining, and

- i) if cleaved from the resin, purifying the peptide prior to the coupling of the reactive group, either directly or via a lysine, to the peptide;
- ii) if not cleaved from the resin, cleaving and purifying the peptide prior to the coupling of the reactive group, either directly or via a lysine, to the peptide.

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~~28.~~ (New) A method as claimed in claim ~~27~~ wherein the reactive group is selected from the group consisting of succinimidyl- and maleimido-containing groups.

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~~29.~~ (New) A method as claimed in claim ~~27~~ wherein the reactive group is coupled to the peptide in the less therapeutically active region of amino acids.

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~~30.~~ (New) A method as claimed in claim ~~28~~ wherein the reactive entity is a maleimido-containing group.

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~~31.~~ (New) A method as claimed in claim ~~27~~ wherein the reactive group is coupled to the peptide via a lysine.

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~~32.~~ (New) A method as claimed in claim ~~27~~ wherein the reactive group is coupled to the carboxy terminal amino acid of the peptide.

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~~33.~~ (New) A method as claimed in claim ~~27~~ wherein the peptide does not contain a cysteine.

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~~34.~~ (New) A method as claimed in claim ~~27~~ wherein the therapeutic peptide contains two cysteines and the peptide is cleaved from the resin, the two cysteines are oxidized to form a disulfide bridge, and the reactive group is coupled to the peptide, either directly or via a lysine.

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~~35.~~ (New) A method as claimed in claim ~~33~~ wherein the peptide is synthesized from the carboxy terminal amino acid.

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~~36.~~ (New) A method of synthesizing a modified therapeutic peptide capable of forming a peptidase-stabilized therapeutic peptide conjugate, the peptide comprising between 3 and 50